REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The undersigned wishes to express appreciation to the Examiner and his supervisor for the very helpful interview of January 28, 2008. The Examiner's Summary adequately reflects the substance of the interview and thus no further comment is believed to be necessary.

The Examiner indicates that claims 6-24 are directed to an invention distinct from that originally claimed. The Examiner contends that the method of claims 6-24 lacks a shared special technical feature with the originally presented invention, stating "while both groups involve the structure of Formula I, recited in instant claim 1, this generic structure is an obvious variant of the prior art, as described below." Applicants respectfully disagree and urge the Examiner to reconsider his position in light of the comments that follow and to examine claims 6-24 in this application. Applicants detail below why the generic structure would not have been obvious over the cited art.

Claim 1 has been revised to define the invention with additional clarity and to delete reference to the ODmab groups. Claim 1 has also been amended to include the limitation that when n=1, at least one of R4 and R5 is OR or N(Y)Z. This revision is supported by the Examples, most if not all of which require at least one of R4 and R5 to be OR and are not both hydroxyl. With this revision, the further proviso relating to glycolate and lactate has been deleted. Claim 2 has been revised to delete the

"derivative of" language. Claim 3 has been cancelled and re-presented in independent form as new claim 28. Claim 27 has been revised to delete the reference to Z4.

Prior to addressing the Examiner's specific concerns, the following comments are offered by way of background.

Applicants have developed methods and prepared compounds for drug development. The compounds of the instant invention present pharmacophoric groups in 3-dimensional arrangements in such a manner that they are suitable for interaction with biological receptors. Each of the appended groups is selected to optimize interaction with a biological receptor. The compounds of the instant invention exhibit drug like properties, being stable under a wide range of biological, metabolic and chemical conditions. Applicants believe that the instant invention is novel and would have been unobvious over the art cited by the Examiner for the reasons detailed below.

Claims 1, 2, 4, 25 and 26 stand rejected under 35 USC 103 as allegedly being obvious over Sas et al. The rejection is traversed.

In rejecting the claims as obvious over Sas et al, the Examiner contends:

1. It would have been obvious to one of ordinary skill in the art to practice the synthetic scheme of Sas et al in order to produce a compound having two dissimilar ethers at positions R2 and R3.

2. One of ordinary skill in the art would have been reasonably motivated to make these compounds because they fall within the general formula described by Sas et al.

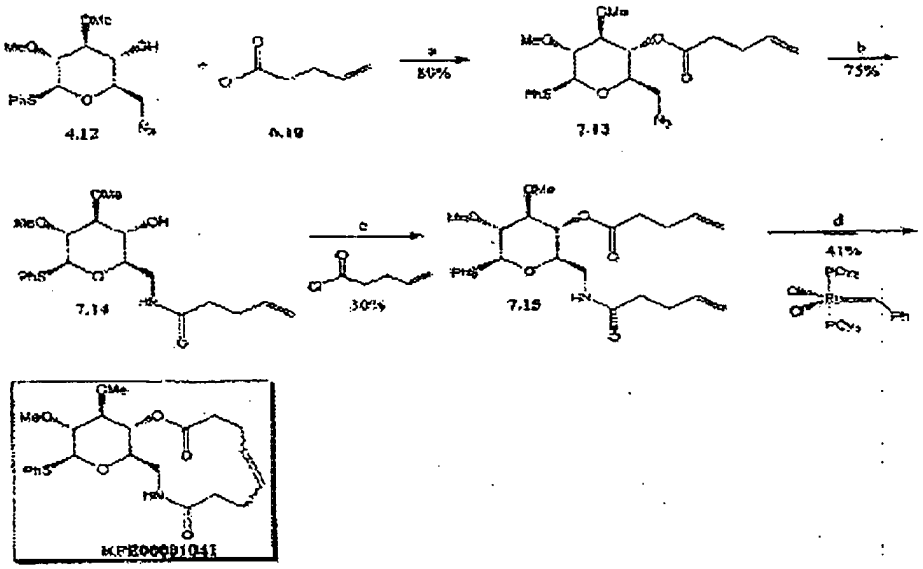
3. One of ordinary skill in the art would reasonably have expected success because all the groups are stable to the synthetic transformations performed in the disclosed synthetic scheme.

Applicants respectfully disagree for the reasons that follow.

Sas et al discloses the preparation and use of carbohydrate-based bicyclic ring structures with antimicrobial and cytostatic activity. The compounds disclosed are molecules comprising a carbohydrate scaffold and an attached ring system which are commonly known as macrolides or ketolides. Clearly, these compounds are macrolides which are known to possess biological activity. In contrast, the present invention relates to significantly smaller molecules comprising a monosaccharide scaffold that is not further condensed because the groups R1 to R5, as defined in instant claim 1, cannot combine together to form a cyclic moiety.

The Examiner identifies compound 7.14 of Figure 10 of Sas et al as falling within the scope of instant claim 1 except for the two methyl groups at R2 and R3. Applicants direct the Examiner's attention to the fact Sas et al does not teach preparation of compounds wherein R2 and R3 are <u>different</u> alkyl ether groups. The synthesis of such compounds is not trivial and nothing in Sas et al would have motivated the skilled person to prepare the compounds of the instant invention.

Figure 10 of Sas et al, reproduced below, shows the derivation of compound 7.14 from the precursor 4.12. While the source of compound 4.12 is not explicitly identified, it appears that this material is prepared from the precursor KPE00001011 shown in Figure 18 (reproduced in part below).



a) pyridine, DMAP, CH_2Cl_2, r.t., 24 h; b) PPh_3 (polystyrene carrier), THF/H_2O, 100/1, r.t., 48 h; c) Et_3N, CH_2Cl_2, r.t., 24 h; d) Grubbs cat 30 mol%, CH_2Cl_2, reflux, 16 h.

FIG. 10

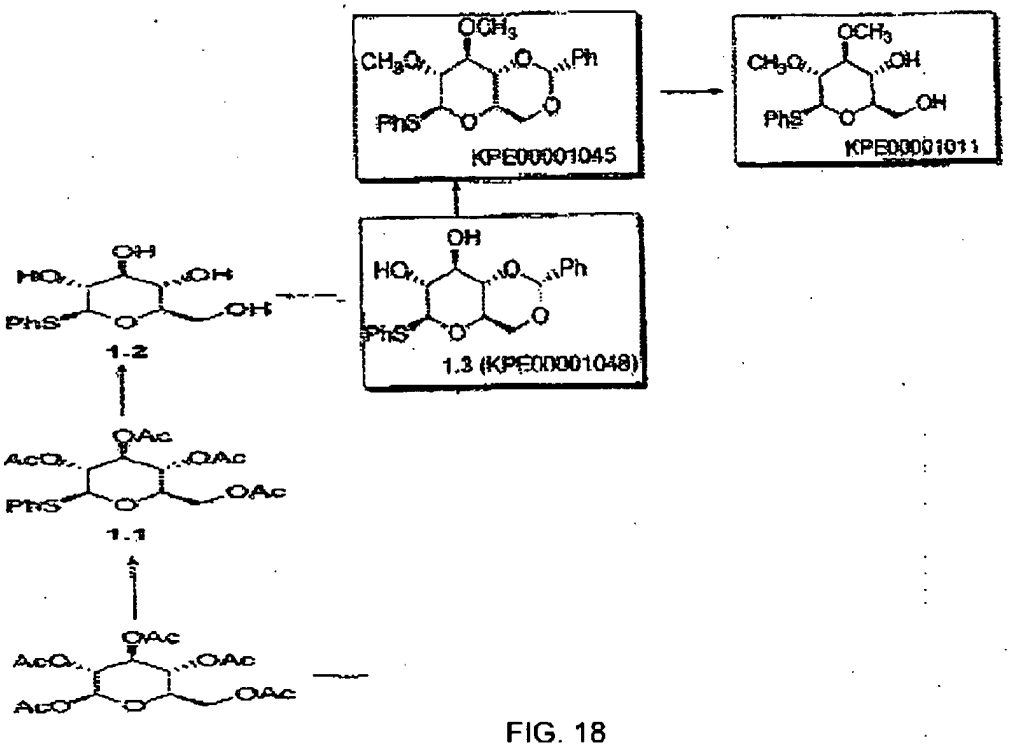


FIG. 18

KPE00001011, in turn, is derived from glucose penta-acetate. The methyl groups at positions R2 and R3 of compound 7.14 are introduced in a single step by the treatment of compound 1.3 with methyl iodide and sodium hydride in DMF as shown in Figure 18 and discussed in the experimental protocol provided in Sas et al. Applicants submit that the reaction scheme shown in Figure 18 of Sas et al, which details the introduction of the two methyl groups, would not have taught one of ordinary skill in the art how to introduce two different groups at R2 and R3.

Furthermore, one of ordinary skill would not have expected to be successful in selectively introducing different groups at positions R2 and R3 by following the teachings of Sas et al because Sas et al teaches the introduction of the two groups in a single chemical transformation which is unable to differentiate between the positions to be methylated.

In contrast to the teachings of Sas et al, Applicants employ monosaccharide scaffolds, which provide an excellent platform to tailor molecular diversity by appending desired substituents at selected positions around the sugar scaffold (Giang Thanh Le et al ; Drug Discovery Today 8, pp 701-709 (2003)). The design strategy relies upon the regioselective introduction of a variety of groups onto a scaffold in a stepwise fashion. As noted in Example 5, the alkylation of the scaffold proceeds over a series of steps. Hence, this strategy requires alkylation over different steps, which is distinguished from the teachings of Sas et al which require introduction of the same alkyl groups (eg, methyl) in one step.

As discussed previously, Sas et al discloses a series of macrolide antibiotics which contain a macrocycle between the C-6 and C-4 positions of a glucose ring. The biological activity of the macrolide antibiotics is largely attributed to the nature of the macrocyclic ring. Sas et al discloses that these antibioticas are inactivated by hydrolysis of the lactone ring (see column 6, lines 43 to 47). The groups at positions R2 and R3 are largely unassociated with biological activity, functioning rather as capping groups for the free hydroxyls.

The introduction of the capping groups is designed to be rapid and the choice of capping group (or, indeed, benzyl at R2 and R3) is largely inconsequential, as evidenced by the almost identical antibacterial activity (shown in Table 4) of compounds KPE00001002 and KPE00001037. KPE00001002 and KPE00001037 differ only in that the '1002 compound has R2 and R3 as methyl and the '1037 compound has R2 and R3 both as benzyl.

To introduce groups of a different nature into the molecules of Sas et al would have been an unnecessary complication without an obvious advantage. To do so would have introduced many additional synthetic steps, which would have been unpredictable in outcome. Therefore, one skilled in the art would not have been motivated to do so based on Sas et al.

Clearly, Sas et al would not have provided any suggestion or motivation to prepare the monosaccharide compounds of the instant invention. It is only with the benefit of hindsight that one could contend otherwise. Furthermore, Sas et al does not teach how to make such compound. Therefore, withdrawal of the rejection is in order and the same is requested.

Claims 1, 2, 4 and 25-27 stand rejected under 35 USC 103 as allegedly being obvious over Johnson et al in view of Carey et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

Johnson et al discloses a process for making aminoalkyl glucosaminide phosphates and disaccharides. The Examiner has identified a specific compound at column 11, lines 16-33 of Johnson et al that is similar to compounds of claim 1 except that the group corresponding to R5 is an O-silyl protecting group and the group corresponding to R2 is an NH-Troc protecting group. Applicants direct attention to the fact that neither silyl nor carbamoyl protecting groups fall within the scope of the instant claims. Indeed, the use of protecting groups, which are by definition labile, is counter to the express purpose of the instant invention, that is, to provide compounds with drug like properties.

Applicants submit that replacing the protecting groups taught in Johnson et al with other protecting groups taught by Carey et al would not have led the skilled person to the instant invention. Indeed, the instant invention is directed towards compounds with stable moieties appended to a monosaccharide scaffold. Such compounds would not be suitable for use in the schemes of Johnson et al because the appended groups are not readily removable, and, therefore, there would be no motivation to prepare compounds of the instant invention in light of the teachings of Johnson et al and Carey et al.

In summary, Johnson et al would have provided no suggestion or motivation to prepare the monosaccharide compounds of the instant invention. Carey et al offers

nothing that would have cured this fundamental failing. Accordingly, withdrawal of the rejection is requested.

Claims 1, 2, 4 and 25-27 stand rejected under 35 USC 103 as allegedly being obvious over Fukase et al in view of Carey et al. The rejection is traversed.

Fukase et al discloses synthesis of Lipid A based on effective use of compounds comprising protecting groups. The protecting groups utilized in the intermediate step in Scheme 3, referred to by the Examiner, include the Fmoc group.

The Examiner points to compound 17 of Fukase et al as falling within the scope of the claims except for the exclusionary proviso. The Examiner contends that compound 17, taken in view of Carey et al would have rendered the instant invention obvious. Applicants respectfully disagree.

Compound 17 of Fukase et al contains an Fmoc group at C-2 which falls outside the scope of the instant invention. Carey et al discloses a range of protecting groups which the Examiner suggests could have been used to replace the Fmoc group thereby yielding a compound falling within the scope of claim 1.

Applicants submit that the arrangement of protecting groups in compound 17 of Fukase et al is not merely a random selection of protecting groups but a special and carefully selected arrangement that allows the synthesis of the desired lipid A. Applicants submit that one of ordinary skill in the art, on viewing Fukase et al in the knowledge of Carey et al, would not have been led to the instant invention.

Compound 17 of Fukase is used to make compound 1. The Fmoc being removed in the conversion from compound 22 to 23. In order to be suitable for this purpose, any replacement for the Fmoc the protecting group on the molecule must survive the

reaction conditions leading to the formation of compound 17 and the subsequent transformations to compound 22. Those conditions are as follows:

1. TMS triflate/ Ethyl silane acetal formation step 13 to 14
2. Tin mediated alkylation step 14 to 15
3. Zn-Cu reduction followed by azidonitration step 15 to 16
4. Borane mediated reductive ring opening step 16 to 17
5. Zn/acetic acid reduction (reduction, acid) step 17 to 18
6. Glutaric anhydride acylation step 18 to 19
7. DIC mediated peptide coupling
8. BF3.dietyl etherate (lewis acid) step 20 to 3
9. TMS-triflate (strong acid/lewis acid) step 3 to 4
10. Zn-Cu / acetic acid (reduction) step 21 to 22
11. Organic base (DBU) step 22 to 23

Additionally, the Fmoc must then be removed under conditions which do not compromise the integrity of the other protecting groups in intermediate 23 so prepared.

Carey et al discloses the following protecting groups for the protection of amines:

i) Cbz (carbobenzyloxycarbamate) – susceptible to conditions 1, 3, 5 and 10; additionally, the conditions required to remove the Cbz group would affect the allyl, alloc and benzyl protecting groups in compound 22

ii) t-Boc (t-butoxycarbamate) – susceptible to conditions 1, 3, 4, 5, 8, 9, 10.

iii) alloc (allyl carbamate) – susceptible to conditions 3, 4, 5, 8, 9, 10; additionally, conditions required to remove the Alloc group would affect the allyl moiety and could not be differentiated from the alloc group on the other saccharidic group.

iv) N-benzyl is extremely inert; the conditions required to remove an N-benzyl group would affect the allyl, alloc and benzyl protecting groups in compound 22.

v) Phthalimide is also extremely inert; the conditions required to remove an N-phthalimide group would affect the allyl, and alloc protecting groups in compound 22 and would cleave the lipid ester functions on the molecule.

vi) Trifluoroacetyl - susceptible to conditions 1, 2, 3, 4, 5, 10; additionally, conditions required to remove the trifuoroacetamide group would affect the alloc moiety and potentially the lipid esters in the molecule.

vii) 4-methoxy-benzenesulfonamide – a special case sulphonamide which is removable by photoactivation and reduction or by strong acid HBr/acetic acid; the conditions required to remove this protecting group would affect both the alloc and allyl protecting groups in compound 22 - in the case of removal with HBr, the benzyl group and the glycosidic bond would also be affected.

It is apparent that there may be other protecting groups for the amine function that could be identified in the art. However, there is no obvious replacement for the Fmoc moiety that would have provided a reasonable expectation of success. Further, Carey et al would have provided no motivation to change the protecting group strategy presented by Fukase et al. Fukase et al aims to produce lipid A analogues and provides a protecting group strategy that meets this aim. In light of the extremely complex requirements for the protecting group strategy, one skilled in the art would not have been motivated to deviate from the teachings of Fukase et al.

As the Examiner appreciates, the molecules disclosed by Fukase et al do not fall within the scope of the instant invention. The claimed molecules were designed to

display drug-like properties. Thus the appended groups were designed to be stable or non-labile. Fukase et al and Carey et al would have taught away from the molecules of the instant invention because the molecules of Fukase et al and the teachings of Carey et al are directed towards protecting groups which are inherently labile or removable.

One skilled in the arty would not have been motivated to prepare compounds of the instant invention by the cited art because to do so would have failed to achieve the aims of Fukase et al.

Withdrawal of the rejection is requested.

Claims 1, 2 and 4 stand provisionally rejected as allegedly representing obviousness-type double patenting over claim 1 of copending Application No 10/419,070. Withdrawal of the rejection is submitted to be in order in view of the above-noted revision of claim 1 to require that at least one of groups R4 and R5 be OR or N(Y)Z when n=1. However, should the Examiner remain unpersuaded, it is requested that this provisional rejection be held in abeyance until the case is otherwise in condition for allowance.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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